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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/995,337	11/27/2001	James Rasmussen	GC22.4-CON	1762

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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	13

DATE MAILED: 10/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/995,337	RASMUSSEN ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This is the First Office Action on the Merits of the application filed 27 November 2001 as a continuation of 08/442,603 filed 05/17/1995, which is a continuation of 08/015,735 filed 02/10/1993, which is a continuation of 07/748,283 filed 08/21/1991, which is a divisional of 07/455,507 filed 12/22/1989, which is a CIP of 07/289,589 12/23/1988. The preliminary amendments filed 16 July 2002and 27 November 2001 have been entered. Claim 32 is pending in the application.

Election/Restrictions

Applicant's election with traverse of Group III in Paper No. 12, filed 22 July 2003, is acknowledged. The traversal is on the ground(s) that the inventions are interrelated and a search of the claims of Group III would necessarily include a search of the claims of Group I and II. This is not found persuasive because the restriction requirement was made on the grounds that the claims are directed to patentably distinct inventions. The argument is unclear because Applicant has provided no explanation of how the inventions are "interrelated" such that the groups are not patentably distinct. With regard to search, a search for the mammal of Group III clearly would not encompass the full scope of the subject matter of Groups I and II. As the Groups cannot be searched coextensively, the search and examination of the additional Groups imposes an undue burden on the Office.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 32 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claim is directed to a mammal comprising a eukaryotic cell comprising a nucleic acid encoding an enzymatically active glucocerebrosidase, wherein said glucocerebrosidase is capable of specifically binding with a human mannose receptor protein. The art teaches that glucocerebrosidase extracted from human placenta is capable of specifically binding with a mannose receptor protein (see Friedman *et al.* (1999) *Blood* 93:2807-2816, especially page 2802 bridging columns 1 and 2, and Figure 1 and the caption thereto). Thus, a human being, and other mammals, as they are found in nature meet all of the limitations of the claim. Therefore, the claims encompass products of nature, which is nonstatutory subject matter. Furthermore, the claimed subject matter is also non-statutory to the extent that the claims encompass genetically modified humans (i.e., a mammal comprising a genetically modified eukaryotic cell). Amending the claims such that they are directed to a non-human mammal comprising a eukaryotic cell comprising a recombinant nucleic acid encoding an enzymatically active glucocerebrosidase, for example, would be remedial.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 32 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: The claims broadly encompass any mammal comprising eukaryotic cell comprising an enzymatically active glucocerebrosidase capable of specifically binding with a human mannose receptor protein. As only those embodiments of the claim wherein the eukaryotic cell comprises a recombinant glucocerebrosidase and the mammal is non-human are considered patentable subject matter, discussion of enablement under 35 U.S.C. §112, first paragraph, will be limited to those embodiments. The specification provides, "the invention is useful for therapeutic treatment of Gaucher's disease by providing a therapeutic amount of the rGCR. By therapeutic amount is meant an amount of rGCR which will cause significant alleviation of clinical symptoms of Gaucher's disease" (paragraph bridging pages 26 and 27). Thus, to be enabled for the claim, the

specification must teach the skilled artisan how to make a non-human mammal capable of producing an amount of rGCR which will cause significant alleviation of clinical symptoms of Gaucher's disease.

State of the prior art and level of predictability in the art: At the time of the effective filing date of the instant application (i.e., 23 December 1988) the recombinant production of proteins in mammals for pharmacological use was in an early stage of development. In reviewing the relevant literature, Houdebine (*Transgen. Res.* (2000) 9:305-320) describes a myriad of obstacles that have been encountered by artisans seeking to express recombinant proteins in mammals at pharmaceutically relevant levels. In the abstract, Houdebine identifies three major sources of unpredictability in the art. First is the unpredictability of transgene expression; second is the unpredictability of proper posttranslational modification; and third is the unpredictable effects of high-level recombinant expression on the host mammal. Significantly, in an article published 12 years after the effective filing date of the instant application, Houdebine teaches, "the mammary gland is presently the only really available animal bioreactor" (page 315, column 1, paragraph 7). Thus, even 12 years after the instant application was filed, methods for pharmaceutically relevant production or recombinant proteins in mammalian organs and tissues outside of mammary gland were unavailable to the skilled artisan. With regard to production of pharmaceutical proteins in milk, Houdebine teaches, "numerous experiments have shown that the level and specificity of expression of a gene construct used as a transgene cannot be easily predicted" (paragraph bridging pages 309-310). In the paragraph bridging the left and right columns on page 311, Houdebine teaches that even the best mammary-specific promoters

available as of 2000 provided inconsistent and unpredictable results when used for expression of recombinant proteins *in vivo*.

Significantly, Houdebine points out that experiments carried out *in vitro* using cultured mammary cells are poor predictors of expression *in vivo*. In the third paragraph in the first column on page 314, Houdebine states, "[cultured mammary] cells can at best predict the intrinsic potency of a construct for transcription but not the level of expression in transgenic animals. The cell lines are not expected to be able to reflect all the events, which mature the proteins post-transcriptionally." Houdebine further teaches that proper posttranslational processing of proteins expressed at pharmaceutically relevant levels is often unpredictable because the mechanisms are dependent on cellular enzymes that are present at variable concentrations in different cell types (paragraph bridging columns 1 and 2 on page 313). Importantly, because proper glycosylation is vital for pharmacological activity of the glucocerebrosidase enzyme (specification, bridging pages 1-2), Houdebine teaches that mammary cells do not always glycosylate recombinant proteins in an appropriate manner even when the protein is naturally secreted in milk in a glycosylated form (see the example of bile salt-stimulated lipase presented in the second full paragraph in the right column on page 313). Houdebine teaches that the reasons why some proteins are not correctly glycosylated are particularly complex and might be related to the superphysiolgical production of the recombinant protein. Furthermore, in the paragraph bridging columns 1 and 2 on page 310, Houdebine teaches that obtaining high-level expression of proteins that are not naturally secreted, such as the instant glucocerebrosidase, is particularly problematic.

When viewed as a whole, the teachings of Houdebine, which are based on a review of the art 12 years after the instant claim was filed, clearly show that obtaining pharmaceutically useful expression of a protein in a mammal was only enabled for a limited set of proteins in mammary tissues, and production of pharmaceutically useful amounts of any given protein in mammary tissue was unpredictable. As the art does not provide teachings that would enable the skilled artisan to make a mammal capable of producing a pharmaceutically useful amount of a glucocerebrosidase, the skilled artisan must rely on the specification for guidance as to how to make the claimed invention without undue experimentation.

Amount of direction provided by the inventor and existence of working examples: The teachings of the instant specification are limited to statements that the invention encompasses mammals comprising a nucleic acid encoding an enzymatically active glucocerebrosidase capable of specifically binding with a human mannose receptor protein and a reduction to practice of an immortalized hamster cell line comprising a recombinant nucleic acid encoding an enzymatically active glucocerebrosidase. There is no teaching of expression constructs that might overcome the art-recognized limitations of available promoters and no teaching of a particular cell type or tissue that would provide pharmaceutically useful expression *in vivo*.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the level of skill in the art is high, it would require undue experimentation to make the instant claimed invention such that it could be used for the purpose set forth in the specification. In essence, the specification teaches the skilled artisan how to express glucocerebrosidase in a cultured cell line, which is not an accepted model of *in vivo* expression, at a level that is not asserted to be pharmaceutically relevant. The specification

provides no teaching at all with respect to which mammals should be used, in which cells or tissues the protein should be expressed, an effective *in vivo* expression vector, or how important limitations such as protein toxicity and improper or inefficient posttranslational processing might be overcome. Given the unpredictability of the art even in the year 2000, the skilled artisan working in 1988 would clearly have to engage in undue experimentation to extend the teachings provided in the specification to make a single species of mammal capable of producing a pharmaceutically useful amount of an enzymatically active glucocerebrosidase capable of specifically binding with a human mannose receptor protein. For this reason, the claims fail to meet the enablement requirement of 35 U.S.C. §112, first paragraph.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 32 is rejected under 35 U.S.C. 102(b) as being anticipated by Sorge *et al.* (1985) *Proc. Natl. Acad. Sci. USA* 82:7289-7293 as evidenced by Friedman *et al.* (*supra*).

To the extent that the claim reads on a mammal comprising a eukaryotic cell comprising a recombinant nucleic acid encoding enzymatically active glucocerebrosidase capable of specifically binding with a human mannose receptor protein, the art provides no anticipatory teachings. However, as described above, the claims also encompass a mammal comprising a native nucleic acid encoding enzymatically active glucocerebrosidase, which Sorge *et al.* demonstrates to include humans by disclosing a human glucocerebrosidase cDNA. Further, as described above, Friedman *et al.* demonstrates that the glucocerebrosidase encoded by humans is

capable of specifically binding with a mannose receptor. Thus, the mammal of Sorge *et al.* anticipates the instant claimed mammal.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER